

---

(12) UK Patent Application (19) GB (11) 2 078 696 A

---

- (21) Application No 8115770  
(22) Date of filing 22 May 1981  
(30) Priority data  
(31) 55/070060  
(32) 28 May 1980  
(33) Japan (JP)  
(43) Application published  
13 Jan 1982  
(51) INT CL<sup>3</sup>  
C01F 11/00  
(52) Domestic classification  
C1A 424 510 530 D37  
D80 G47 G47D37 G47D80  
PG2  
(56) Documents cited  
GB 1554943  
GB 1484781  
GB 1421531  
GB 1004352  
(58) Field of search  
C1A  
(71) Applicant  
Mitsubishi Mining &  
Cement Company  
Limited,  
No. 5-1, 1-chome,  
Marunouchi, Chiyoda-ku,  
Tokyo, Japan  
(72) Inventors  
Yoshiaki Fukuda,  
Takao Inukai,  
Hiroyasu Takeuchi,  
Mikiya Ono  
(74) Agents  
Serjeants,  
25 The Crescent, King  
Street, Leicester, LE1 6RX

(54) **Porous Calcium Phosphate  
Body**

(57) A filler for defects or hollow portions of bones comprises a porous body of a calcium phosphate compound, such as hydroxyapatite. The pores in the body are formed by a three-dimensional network of void

channels, each channel being of varying width along its length. The maximum width of any channel is 3.00 mm and the minimum width is 0.05 mm. The porosity of the porous body is from 40% to 97%, providing a filler into the void channels of which bone forming constituents of living bodies can easily penetrate and create new bone growth.

# **SPECIFICATION** **Filler for Implanting in Defects or Hollow** **Portions of Bones**

The present invention relates to an inorganic  
5 filler to be used to fill in defects or hollow portions  
of bones formed by operations to remove bone  
tumor or other causes in the bones of living  
bodies, to promote the formation of new bone  
tissue at the filled portion and to coalesce with  
10 the bone tissue after the injured portion is  
completely cured.

In the surgical or orthopedic field, defects or  
hollow portions of bones are frequently formed by  
highly complicated fractures or operations to  
15 remove bone tumor, and such defects or hollow  
portions should be cured by symphysis. In a prior  
art method, a cancellous bone is taken up from  
flank bones or other bones of the patient to be  
filled in the injured portion of bone so as to  
20 promote the cure of bone tissue. However, this  
prior art method is disadvantageous in that the  
patient suffers a greater pain and cumbersome  
labours are necessitated in the operation, since a  
bone tissue other than the injured portion is taken  
25 out for use. Moreover, a sufficient amount of  
autoplastic bone cannot be always taken up from  
the patient's body for filling in a large defect or  
hollow portion of bone, and a certain substitute  
material is required to supplement the shortage of  
30 the required bone tissue in such a case.

Other than the method of autoplastic filling,  
there are methods of homogeneous bone  
implantation and heterogeneous bone  
implantation. As to the homogeneous bone  
35 implantation method, the use of frozen bones and  
decalcified bones have been investigated but  
have not yet reached the stage of clinical practice.  
In the heterogeneous bone implantation method,  
a so-called keel bone, which is prepared by  
40 removing proteins from bones of cattle, is used in  
some cases. However, both of these known  
methods are not only accompanied with foreign  
body reactions but also lack osteogenic capacity,  
so that the post-operational course is not always  
45 good.

Accordingly, there is an increasing demand for  
an artificial filler material for filling or implanting  
in defects or hollow portions of bones. This must  
have a good compatibility with the living body  
50 and a high osteogenic capacity to promote the  
bone-forming reaction at and around the filled  
portion so as to accelerate curing of the structure  
and functioning of the injured bone tissue.

Various metals and plastics materials have  
55 hitherto been used as the substitute materials for  
hard tissues of the living body. However, these  
conventional materials are apt to dissolve or  
otherwise deteriorate under the severe  
environment of the living body and are often  
60 accompanied by poisonous actions or foreign  
body reactions. For these reasons, ceramics,  
which have improved compatibilities with living  
body, have been increasingly used in recent years.  
Inter alia at the latest time, an artificial bone and

65 an artificial radix dentis comprising a sintered  
body or a single crystalline structure of alumina,  
carbon, calcium tertiary phosphate ( $\text{Ca}(\text{PO}_4)_2$ ) or  
hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ ) have been  
proposed. It has been reported that these are  
70 excellent in their compatibility with the living  
body.

Although it has been tried to implant the above  
mentioned sintered body or single crystalline  
structure in a defect or hollow portion of bone to  
be remedied, difficulties are encountered when  
75 the sintered body or single crystalline structure  
has to be machined to create a snug fit into the  
bone defect which may have a complicated shape  
rather than a simple and constant shape.  
80 Moreover, even if such a sintered body or single  
crystallite structure could be implanted in a  
defect, absorption of bone tissue would occur at  
the vicinity of the implanted portion since the  
sintered body or single crystalline structure is  
85 generally substantially harder than the  
surrounding bone tissue to give a stimulus to the  
surrounding living tissue. As a result, loosening or  
other problems occur, so that a sintered body or  
single crystalline structure of the aforementioned  
90 kind has not yet reached the stage of practical  
use.

It has been proposed to make a porous body of  
a sintered material by the mechanical method of  
first moulding a mixture of the powder to be  
95 sintered and a portion of combustible fibres,  
followed by sintering so as to obtain a porous  
body having a shape which can be snugly fitted in  
a defect or hollow portion of bone. However there  
are two serious practical problems. The first is the  
100 difficulty of moulding mixtures with a combustible  
fibre content high enough to produce a  
sufficiently porous sintered body. The second is  
that the fragility of a porous sintered ceramic  
body increases and its machinability decreases, as  
105 the total pore volume of the sintered body  
increases. Thus sintered bodies of ceramics  
having sufficiently high porosities have not yet  
been manufactured commercially. Because of the  
lack in porosity due to the difficulties as  
110 aforementioned bone forming constituents can  
scarcely penetrate the rather solid filler, so that  
coalescence of the filler with the living tissues to  
form new bone is very slow.

According to the present invention, there is  
115 provided a filler for filling in defects or hollow  
portions of bones, comprising a porous body of a  
calcium phosphate compound in which a plurality  
of channels communicate with each other to form  
a three-dimensional network of voids, wherein  
120 each channel has along its length a non-constant  
width of between 3.00 mm and 0.05 mm, and the  
porosity of the body is from 40% to 97%.

It has been found that the growth of new bone  
is promoted by a filler according to the invention,  
125 with the new bone being grown in a defect or  
hollow portion of bone from the portion at which  
the filler is in contact with the old bone.

The calcium phosphate compounds which may  
be used in the present invention include calcium

secondary phosphate ( $\text{CaHPO}_4$ ) and its dihydrate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ), calcium tertiary phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ ), calcium tetrakisphosphate ( $\text{Ca}_4\text{O}(\text{PO}_4)_2$ ), calcium undeca-oxo-tetrakisphosphate ( $\text{Ca}_3\text{P}_4\text{O}_{11}$ ), calcium metaphosphate ( $\text{Ca}(\text{PO}_3)_2$ ), calcium pyrophosphate ( $\text{Ca}_2\text{P}_2\text{O}_7$ ) and calcium dihydrogenphosphate monohydrate ( $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ ). These compounds may be used individually or in a form of mixture containing two or more of them. Amongst the compounds set forth above, calcium tertiary phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ ) and calcium tetrakisphosphate ( $\text{Ca}_4\text{O}(\text{PO}_4)_2$ ) are preferable compounds, since growth of new bone is particularly accelerated when any one or more of these three compounds is used. The most preferable compound to promote growth of new bone is hydroxyapatite, particularly hydroxyapatite which is baked at a temperature of higher than  $500^\circ\text{C}$ , preferably  $700$  to  $1250^\circ\text{C}$ . The upper limit temperature of baking operation is not critical but should be controlled not to exceed the decomposition temperature of hydroxyapatite. The calcium phosphate compounds used in the present invention may be either artificially synthesized compounds produced by any known process or compounds of natural origin obtained from human or animal bones.

In the filler of the invention, the internal areas of the channels or void cavities is increased so that increased quantities of calcium and phosphoric ions are dissolved internally of the porous body. An increase in the dissolved quantities of calcium and phosphoric ions is one of the principal advantages of the present invention. As a result of this increase, the formation of new bones is commenced rapidly with new bones growing on the surfaces of bone forming tissues, including collagen, which have penetrated into the channels or cavities. Since the width of each channel varies randomly along its length, numerous concave and convex portions, providing recesses and projections, are formed along the internal surface of each channel. The present invention is based on the observation that there is a tendency for the bone forming substances to adhere initially to or at the vicinities or projections in the channels while being accompanied with osteoblasts, and that new bones begin to grow from the projections at which the bone forming substances and osteoblasts adhere. In addition, in a filler according to the present invention the void cavities or channels in the porous body communicate with each other to form a three-dimensional network. Accordingly, the bone forming constituents entering the void cavities can penetrate deeper into and finally throughout all regions of the three-dimensional network. Naturally it will be understood that although the void cavities or channels communicate with each other to an extent that a generally cross-linked and three-dimensional structure of void channels

is formed through the porous body, some of the channels or cavities may be closed, resulting in a few closed cells.

The maximum dimension width of each channel in any direction is less than 3.00 mm, and the minimum dimension thereof is more than 0.05 mm. It has been found that if the maximum width were to exceed 3.00 mm, a prolonged period of time would be required for the bone tissue of autoplasty or self-origin to grow and fill in the cavities. On the other hand, if the minimum width were to be less than 0.05 mm, penetration of bone forming constituents, such as collagen, into the cavities of the porous body would be prevented or blocked at the too narrow portions. As a result, the bone forming constituents would not proceed or grow through the blocked or clogged portions, leading to formation of hollow portions in which new bone growth does not occur.

The porosity of the filler according to this invention is from 40% to 97% pore volume. If the porosity were less than 40%, an excessively long time would be required for the bone tissue and the filler to coalesce with each other to form a unified body. Moreover, the machinability of such a dense filler would be reduced to an extent to make it impossible to shape the filler to be snugly fitted in a defect or hollow portion of bone by machining. On the other hand, if the porosity were to exceed 97%, the bulk or volume of newly formed bone would be deficient due to lack of filler material, resulting in an unsatisfactory curing effect. Namely, a longer time would be required for the remedy of the impaired bone portion because the quantity of calcium phosphate implanted would be too small.

The filler according to the present invention may be prepared by a process comprising first impregnating a slurry of a calcium phosphate compound into an organic porous body having a substantially continuous cavity or cavities and having a three-dimensional network structure, with the width distribution required in the final filler. The slurry of calcium phosphate compound is then dried, and the material of the organic porous body removed by heating or other means.

When the filler according to the present invention is filled or implanted in a defect or hollow portion of bone, living bone forming constituents such as collagen and body liquids will penetrate into the pores of network structure of the porous body until they are diffused uniformly throughout the network structure. The filler of the invention does not cause any foreign matter reaction and facilitates rapid formation of new bone. Furthermore, the filler *per se* is absorbed in the living body and gradually by the autoplasmic bone.

The filler of the invention can be used not only for filling in defects or hollow portions of bones formed by surgical or arthroplasty operation, but also for filling cavities formed by dental caries or by a tooth extraction operation or in a defect caused by alveolar pyorrhea.

### Examples

The following Examples illustrate the invention.

#### Example 1

Slurries of calcium tertiary phosphate, calcium tetraphosphate and hydroxyapatite were prepared. Each of the slurries of calcium tertiary phosphate and calcium tetraphosphate was synthetically prepared by the wet process followed by pulverization in a pot mill for over 40 hours in the wet state. The slurry of hydroxyapatite was prepared by the wet process. A porous substrate body made of an organic material and having continuous pores was impregnated with each of said three slurries. The slurry impregnated in the porous body was dried and then baked at 1000°C for three hours to burn away the organic material. As a result, a porous body made of each calcium phosphate compound was formed.

From each calcium phosphate compound, five kinds of porous bodies were prepared by controlling the dimensions of channels of non-constant width which form the pores within the body. The porous body included pores having a maximum width of 5 mm and a minimum width of 3 mm. The second to fourth porous bodies included pores having, respectively, a maximum width of 3.0, 0.5 and 0.07 mm and a minimum width of 1.5, 0.2 and 0.05 mm. The fifth porous body included pores having a maximum width of 0.1 mm and a minimum width of 0.007 mm. The porosities of all of these porous bodies ranged within 68 to 73%.

Each porous body was filled or implanted in a defect of bone (about 6mm $\phi$  x 5 mmL) artificially scooped out of a femur of a living dog which was bred after then, and the course of healing and new bone growth was observed. As of three weeks after the implantation operation, new bones were formed in each of the porous bodies except the fifth (which was the body including pores having a maximum width of 0.01 mm and a minimum width of 0.007 mm. However, in the fifth porous body no appreciable formation of new bones was observed in the void cavities internally of the pores.

Observation after three months from the implantation operation revealed that large quantities of new bones had been formed in the void channels of the second to fourth porous bodies. In these three porous bodies, almost all of the filler materials were substituted by the living bone tissues and the defects were coalesced practically to form a unified continuation of the neighbouring unimpaired bone tissue. Scattering void spaces were observed here and there in the pores of the first and fifth porous bodies.

#### Example 2

Similarly to Example 1, using hydroxyapatite synthesized through the wet process, four different porous bodies were prepared having respective porosities of 20%, 40%, 70% and 97%. The maximum width of the channels providing the

pores of the respective porous bodies was controlled to be within the range of 2 to 1 mm, and the minimum width thereof was controlled to be within the range of 0.8 to 0.1 mm. Each of the resulting porous bodies was implanted in an artificially scooped defect (4 mm $\phi$  x 5 mmL) of a femur of a living dog, and the course of healing and new bone growth was observed.

An attempt was made to prepare a porous body having a porosity of 99% according to a similar process, but this body collapsed due to its lack of inherent rigidity during the step of machining it to be snugly received by the cavity of the defect.

The porous body having a porosity of 20% was also difficult to shape at this step of machining. On examination three months after the implantation, it was found that the bodies had coalesced with the living bone tissues except in the case where a porous body having a porosity of 20% was used. In this latter case the filler has been adhered to the bone tissue at the zones contacting with the surrounding original living bone tissues, but no appreciable coalescence was observed internally of the channels of the porous body.

#### Example 3

Similarly to Example 1, using hydroxyapatite synthesized by the wet process, six porous bodies were prepared by impregnating a hydroxyapatite slurry into pores of substrate bodies of an organic material followed by baking to burn away the organic material. Baking was effected for an hour at a temperature of 300°C, 500°C, 700°C, 1000°C, 1250°C and 1350°C, respectively. The maximum width of the void channels of the resulting porous bodies was within the range of 0.5 to 0.4 mm, and the minimum width thereof was within the range of 0.3 to 0.2 mm. Each porous body was implanted in an artificially scooped defect (4 mm $\phi$  x 5 mmL) of a femur of a living dog, and the course of healing and new bone growth was observed.

It was observed that new bones had been formed in the void channels of all of the respective porous bodies after a lapse of three weeks after implantation. However, there was substantial new bone growth in the porous bodies which had been baked at temperatures higher than 500°C, and particularly remarkable formation or growth of new bones was observed in the channels of porous bodies which had been baked at a temperature of from 700°C to 1250°C.

### Claims

1. A filler for filling in defects or hollow portions of bones, comprising a porous body of a calcium phosphate compound in which a plurality of channels communicate with each other to form a three-dimensional network of voids, wherein each channel has along its length a non-constant width of between 3.00 mm and 0.05 mm, and the porosity of the body is from 40% to 97%.

2. A filler according to claim 1, wherein the calcium phosphate compound is calcium secondary phosphate ( $\text{CaHPO}_4$ ), calcium secondary phosphate dihydrate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ),  
5 calcium tertiary phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ ), calcium tetraphosphate ( $\text{Ca}_4\text{O}(\text{PO}_4)_2$ ), calcium hendecaoxo-tetraphosphate ( $\text{Ca}_3\text{P}_4\text{O}_{11}$ ), calcium methaphosphate ( $\text{Ca}(\text{PO}_3)_2$ ) calcium  
10 pyrophosphate ( $\text{Ca}_2\text{P}_2\text{O}_7$ ), calcium dihydrogenphosphate monohydrate ( $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ ) or a mixture of two or more of the above compounds.

3. A filler according to claim 2, wherein the  
15 calcium compound is calcium tertiary phosphate, hydroxyapatite, calcium tetraphosphate or a mixture thereof.

4. A filler according to claim 3, wherein the

- 20 calcium compound is hydroxyapatite that has been baked at a temperature of higher than  $500^\circ\text{C}$ .

5. A filler according to claim 4, wherein the hydroxyapatite has been baked at a temperature of from  $700^\circ\text{C}$  to  $1250^\circ\text{C}$ .

- 25 6. A filler according to any of the preceding claims, wherein the calcium phosphate compound has been synthesized by the dry process.

7. A filler according to any of claims 1 to 5,  
30 wherein the calcium phosphate compound has been synthesized by the wet process.

8. A filler according to any preceding claim wherein the calcium phosphate compound has been prepared from bone tissue.

- 35 9. A filler according to claim 1, substantially as disclosed in any of the Examples herein.